REMARKS

Entry of the foregoing, further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.114, are respectfully requested.

Personal Interview

Applicants and their representative thank the Examiner for the courtesies extended by Examiner Slobodyansky during the personal interview conducted on February 14, 2005. As is correctly reflected in the Interview Summary mailed February 16, 2005, the pending claims, possible claim amendments, the proposed substitute Specification, and the proposed substitute Sequence Listing were discussed. *See Statement of the Substance of the Interview filed March 14, 2005.*

Status

As is correctly reflected in the Office Action Summary mailed July 1, 2004, Claims 27, 29-40, 45, and 47-53 are pending. As indicated in the Advisory Action mailed January 13, 2005, Claims 27, 29-40, 45, and 47-53 stand rejected.

Acknowledgement to Applicants' claim for foreign priority under 35 U.S.C. § 119(a)-(d) was made in the Official Action mailed October 10, 2001, and all certified copies of the priority documents have been received from the International Bureau.

The Draftsman has objected to the left margin of Figures 2, 3, and 5, as noted in the Official Action mailed June 26, 2001, at Page 4. Formal drawings were submitted by Applicants on July 26, 2001. Applicants respectfully request an

indication in the next Office Action Summary as to whether the drawings filed July 26, 2001, are accepted by the Examiner.

Summary of Claim Amendments

By the foregoing amendments, Applicants have, solely for ease of comprehension, cancelled pending Claims 27, 29-40, 45, 47-53, *i.e.*, Applicants have cancelled Claims 1-53, and have presented a new set of claims numbered 54-97. Appendix A, attached hereto, correlates Claims 54-97 to the previously-pending claims and/or provides at least one instance of support found in the Specification, including the original claims and the figures. Accordingly, no new matter has been added.

Substitute Specification

Throughout prosecution of the instant application, the Examiner has indicated that, for example, "the specification is written in a way which precludes a complete and clear understanding of the invention and therefore its full and diligent examination." *See Official Action mailed September 29, 2003, Page 4.* Applicants respectfully disagree.

However, in an effort to advance prosecution, Applicants attach herewith, pursuant to 37 C.F.R. § 1.125(b), a clean Substitute Specification as well as a marked-up Substitute Specification. The Substitute Specification does not include new matter. The Substitute Specification merely corrects minor, linguistic, and/or clerical matters. Support for these amendments may be found in the original Specification.

In addition, the paragraph at page 15 lines 19-25, has been amended to correct an obvious clerical error to include the phrase "the amino acid at position 34, Lys, of GLP-1 has been substituted with Arg." The paragraph formerly was an inadvertentl copy of the paragraph appearing at page 15, lines 1-6, rather than the clearly intended conclusion of the progression of paragraphs that begins at page 13, line 26, which systematically describe the possible combinations of particular substitutions at positions 8, 24, 34 and 36 of GLP-1(7-37) and GLP-1(7-36) that are described individually in the paragraphs between page 13, line 26, and page 14, line 3 and in combination thereafter.

> An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. I*n re Oda*, 443 F.2d 1200, 170 U.S.P.Q. 268 (C.C.P.A. 1971). M.P.E.P. § 2163.07.

The Substitute Sequence listing includes as SEQ ID NOS: 69 and 70, sequences representing the variations described in the paragraph at page 15 lines 19-25.

IN THE ABOVE AS IN THE FOLLOWING REMARKS, ALL REFERENCES TO THE SPECIFICATION REFER TO THE ATTACHED CLEAN COPY OF THE SUBSTITUTE SPECIFICATION.

APPLICANTS' INVENTION

Before turning to the substance of the foregoing claim amendments and rejections of record, Applicants wish to clarify and/or reiterate certain issues.

Applicants' Process Is Designed To Increase Recovery of Desired Peptides

As stated in Applicants' Specification, prior to Applicants' invention, producing peptides on an industrial scale brought about many difficulties, including: the

solubility and gelling of the peptide of interest due to the conditions required for cleaving and modification reactions; the concentration of sample required to be loaded onto the column in chromatographic processes; elution conditions of the column; and stability following elution. *See, e.g., Page 2, Lines 12-19.* Most of these difficulties resulted from the native physicochemical properties of the peptide of interest. *See, e.g., Page 2, Lines 20-21.*

As an example, GLP-1(7-37) can easily gel or aggregate during purification, resulting in markedly reduced recovery and incapability of resin regeneration. *See Page 4, Lines 1-13.* While the gelling can be cured by solubilizing it at a pH of 10 or higher and purification can result, undesirable modifications and conformational changes come about. *See Page 4, Lines 13-18.* As another example, the amidated peptide GLP-1(7-36)NH_2 experiences problems due to the amidation reaction. *See Page 4, Lines 19-30.* GLP-1(7-36)NH_2 formed by precipitating GLP-1(7-37) also coprecipitates, causing production problems because the enzyme reactions do not proceed fully. *See Page 4, Lines 31-34.* Moreover, GLP-1(7-36) tends to aggregate in handling during the column step, resulting in purification problems. *See Page 4, Line 43 to Page 5, Line 4.*

Applicants' Process Alleviates Low Recovery By Relying On Helper Peptides And, If Desired, Protective Peptides

Applicants' process alleviates the foregoing problems by expressing the peptides of interest with the assistance of helper peptides. "The addition of the helper peptides *transiently* changes the physicochemical properties of the peptide of interest" so that the foregoing problems are not experienced "which enhances yield,

promotes efficiency of recovery, and purification of the peptide of interest." *See Page 5, Lines 13-20* (emphasis added).

Applicants' process calls upon a helper peptide prepared based on the native characteristics of the peptide of interest. For example, when the isoelectric point of the peptide of interest is neutral to weak acid and the optimum pH during production is also neutral to weak acid (making the solubility of the peptide of interest under such a pH too low), the helper peptide is preferably designed so that the isoelectric point of the peptide of interest attached to the helper peptide ("AB" or "BA" depicted below) is *transiently* changed to 8-12, and preferably 9-11. *See Page 11, Lines 15-26.* The foregoing transient change in isoelectric point allows for production of the peptide of interest free from the production difficulties experienced prior to Applicants' process.

When the peptide of interest having a helper peptide added thereto is highly expressed, production of the peptide of interest can be increased by adding a protective peptide ("C" depicted below) and expressing it according to conventional methods. *See Page 20, Lines 4-18.*

Figure 1 Summarizes Applicants' Process

Figure 1 sets forth Applicants' process. A narration of Figure 1 may be as follows:

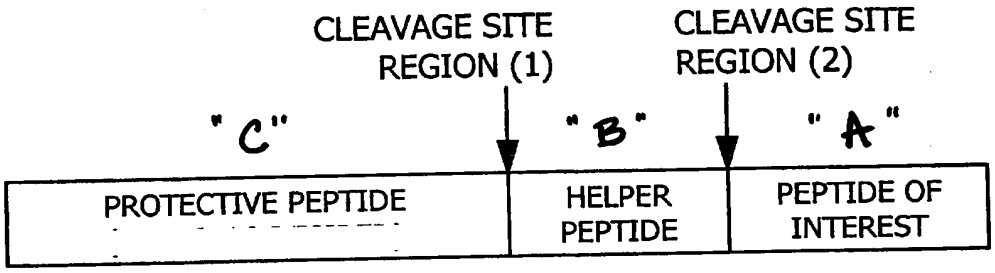
Applicants' process relies on a fusion protein having a peptide of interest ("A") connected to a helper peptide ("B") via a cleavage site. A protective peptide ("C") is also added, via another cleavage site, to the peptide of interest connected to a helper peptide.

Note, the order of these peptides within the fusion protein may be any one of (1)-(4):

(1)	C	B	A	
(2)		B	A	C
(3)	C	A	B	
(4)		A	B	C

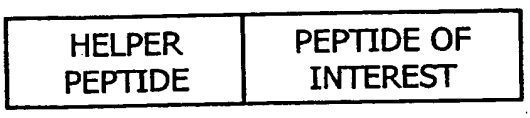
Put differently, Applicants' process requires that "A" and "B" are directly connected via cleavage site, be it A-B (options (3) and (4) above) or B-A (options (1) and (2) above). "C" is attached either before or after the A-B/B-A unit.

Applicants' process first requires culturing cells transformed with the fusion protein. In Figure 1, option (1) is depicted (with Protective Peptide C):



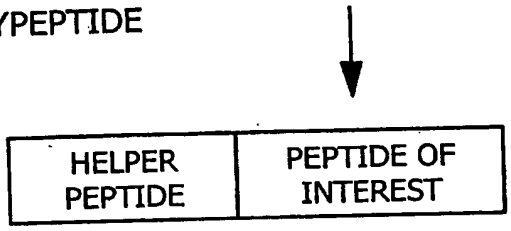
Applicants' process then requires cleaving A-B from C:

(1) WHEN THE PROTECTIVE PEPTIDE IS PRESENT, CLEAVAGE OF SAID PEPTIDE



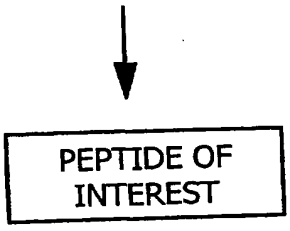
A-B may then be modified:

(2) MODIFICATION OF THE POLYPEPTIDE OF INTEREST AS DESIRED



Applicants' process then requires cleaving B from A, leaving A – the peptide of interest:

(3) CLEAVAGE OF HELPER PEPTIDE



Turning now to issues raised in the Final Official Action mailed July 1, 2004, the Advisory Action mailed January 13, 2005, and points raised at the personal interview, Applicants offer the following:

Objections to the Specification

In the Official Action mailed July 1, 2004, the Examiner objected to the Specification. *See Official Action mailed July 1, 2004, Pages 2-3.*

Use of Brackets

The Examiner objected to the prior use of brackets, rather than parentheses. Not to acquiesce in the Examiner's objections, but solely to facilitate prosecution, Applicants hereby submit both a clean and marked-up Substitute Specification. In the Substitute Specification, the use of brackets has been eliminated. In addition, Applicants now clearly define specific entities at their first citation and denote such entities in quotation marks. *See, e.g., Discussion Below Regarding The Symbol "RHHGP(G)."*

Former SEQ ID NO:25

Regarding what had been SEQ ID NO:25, the Examiner will note that this identifier is not found in the Substitute Specification. As discussed in greater detail below, specific entities that appear to be nucleotide/amino acid sequences are not, in fact, sequences, but instead are merely symbols. For example, the symbol "RHHGP(G)" is the symbol for GLP-1(7-37). GLP-1 (7-37) is a peptide wherein the 6 amino acids from the N-terminus of GLP-1 have been deleted. *See Page 2, Lines 27-29.* Accordingly, "SEQ ID NO:25" is not found in new Claims 54-134.

SEQ ID NO:8

The Examiner indicated that SEQ ID NO:8 is described as an "amino acid sequence containing a site cleaved by Kex2 Protease," but that SEQ ID NO:8 does not appear to contain such a site. *See Official Action mailed July 1, 2004, Page 3.* Applicants respectfully disagree.

The Specification states that the following amino acid sequences are recognized by Kex2: Lys-Arg = K-R; Arg-Arg = R-R; and Pro-Arg = P-R. *See Page 19, Lines 8-13.* Amino acids 4 and 5 of SEQ ID NO:8 are, respectively, Lys-Arg = K-R. Therefore, Applicants respectfully submit that SEQ ID NO:8 does indeed contain "a site cleaved by Kex2 Protease." Applicants respectfully request withdrawal of this objection.

GLP-1

Finally, Applicants note that the Specification as-filed does recite "glucagon-like peptide-1" as the full-spelling of "GLP-1," on Page 2, Lines 20-22 of the original Specification. This is the first instance in the Specification of the abbreviation "GLP-1." However, in an effort to expedite prosecution in this matter, Applicants have amended the paragraph beginning at Page 2, Line 22, to read ("GLP-1") immediately following the first recitation of human glucagon-like peptide-1.

Objections to the Claims

With regard to Applicants' previous claim amendments whereby the phrase "helper peptide unit" was added, the Office asserts that the term "unit" is not present in the Specification. *See Official Action mailed July 1, 2004, Page 3.* Applicants respectfully disagree. While the word "unit" may not be found in the original

Specification, the concept of a peptide of interest being attached to a helper peptide, thereby forming a unit, was present. However, solely to advance prosecution and not to acquiesce in this objection, new Claims 54-134 do not recite the objected-to term "unit."

Regarding "GLP-1," please refer to the final paragraph in the preceding "Objections to the Specification" section.

Comments On New Claims

Applicants wish to respectfully draw the Examiner's attention to several attributes of new Claims 54-97.

First, independent Claim 54 (patterned off of previous Claim 29) sets forth Applicants' process. Applicants have tailored the language of Claim 54 to more accurately and clearly reflect their process. For example, step (1) of the process now states that the fusion protein comprises (a) a protective peptide, and (b) a peptide of interest connected to a helper peptide via a cleavage site. Part (1) further states that prior to use in the fusion protein, the protective peptide, peptide of interest, and helper peptide each have a different isoelectric point. In addition, Part (1) specifies that the isoelectric point of the peptide of interest connected to a helper peptide ("BA" or "AB" as described above) is between 8 and 12. Part (1) continues to specify that the helper peptide has 5-50 amino acids. Parts (2)-(4) have been tailored to more accurately and clearly reflect Applicants' process, as depicted in Figure 1.

New Claims 78-81 build upon Claim 54 yet specify the four options ("(1)" to "(4)" described above with respect to Figure 1), or orders, from N-terminus to C-

terminus, that the protective peptide, helper peptide, and peptide of interest may follow.

Claims 55-59 describe specific attributes of the protective peptide and the purification process. Claims 60-61 provide attributes of the cells cultured in step (1) of Applicants' process. Claims 62-66 set forth attributes of the peptide of interest. Claims 67-71 pertain to Applicants' process where the modification is amidation. Claim 72 is directed to expression vectors comprising the fusion proteins used in Applicants' process. Claims 73-77 address cells transformed with the expression vectors.

Claims 82-89 are directed to isolated amino acids of: GP97ompPR protein encoded by pGP97ompPR (Claims 82, 83 – *See* Figure 7, SEQ ID NO:20); a protein encoded by pG117S4HR6GLP-1 (Claims 84, 85 – *See* Figure 11, SEQ ID NO:21); a protein encoded by pGP117S4HompRHKR (Claims 86, 87 – *See* Figure 12, SEQ ID NO:22); and a protein encoded by pGP117S4HompRHPR (Claims 88, 89 – *See* Figure 13, SEQ ID NO:23).

Claims 90 and 91 are directed to, respectively, fusion proteins wherein the helper peptide contains GCHHHH (SEQ ID NO:5) as described in Example 12A and SDHKR (SEQ ID NO:8) as described in Example 12B.

Claim 92 is directed to GLP-1(7-36)NH_2 (SEQ ID NO:27). Claim 93 is directed to β-gal97S, the protective protein prepared from the 97 amino acids of the N-terminal region of *E. coli* β-galactosidase and corresponding to the amino acid sequence from the first following Met to the Ala at position 98 in Figure 7 (SEQ ID NO:20).

Claims 94-97 are directed to the process of Claim 54, wherein the peptide of interest is one of the peptides of SEQ ID NOS: 27-70, particularly 27 or 28, or the fusion peptide is as described in one of claims 82-91or 93.

Rejections Under 35 U.S.C. § 112, First Paragraph

Written Description

Turning now to the pending rejections, Claims 27, 29-40, 45 and 47-53 were rejected under 35 U.S.C. § 112, First Paragraph, as purportedly lacking written description. *See Final Official Action mailed July 1, 2004, Pages 4-6.* The Office asserts that the rejected claims recite a genus of peptides of interest, a genus of helper peptides, and a genus of protective peptides, and that these genera encompass an infinite number of peptides of any structure and from any source, as long as the isoelectric point of the fusion protein is between 8-12. *Id. at Page 4.* Claims 38-40, 45, 50 and 51 were also rejected as directed to a peptide of interest, GLP-1 derivatives. The Office asserts that because the number of allowed substitutions, additions and/or deletions is not limited, the GLP-1 derivative can have an amino acid sequence with an unknown homology to human GLP-1. Applicants respectfully traverse these rejections.

Not to acquiesce in the Examiner's rejections, but solely to facilitate prosecution, Applicants have canceled rejected Claims 27, 29-40, 45 and 47-53 by the foregoing amendments. Accordingly, the 35 U.S.C. § 112, First Paragraph, written description rejections have now been rendered moot.

Applicants respectfully submit that new Claims 54-97 clearly reflect that Applicants, at the time of filing, were in possession of the claimed invention. *See*

M.P.E.P. § 2163.02 (stating, citing *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989), "An objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.'"). As elaborated upon above, the claimed invention is a *process*. The process calls upon a helper peptide attached to the peptide of interest, and a protective peptide, to *transiently change* the physicochemical properties of the peptide of interest so as to avoid production and purification difficulties associated with the native physicochemical properties thereof.

Applicants' Specification instructs those of skill in the art how to select and combine the helper peptide and protective peptide based upon the native physicochemical attributes of the peptide of interest. As explained above, Applicants' Specification provides the example of when the isoelectric point of the peptide of interest is neutral to weak acid and the optimum pH during production is also neutral to weak acid (making the solubility of the peptide of interest under such a pH too low), the helper peptide is preferably designed so that the isoelectric point of the peptide of interest attached to the helper peptide ("AB" or "BA," as depicted above) is *transiently* changed to 8-12, and preferably 9-11. *See Page 11, Lines 15-26.* The foregoing transient change in isoelectric point allows for production of the peptide of interest free from the production difficulties experienced prior to Applicants' process.

Applicants' Specification enumerates a number of peptides of interest that may be employed in Applicants' process. *See, e.g., Page 12, Lines 1-33.* Applicants' Specification also describes requirements for the helper peptides. *See, e.g., Page 11, Lines 15-33.* The protective peptides are also described. *See, e.g.,*

Page 20, Line 4 to Page 21, Line 5. Moreover, attributes of the modification reactions that may occur are also described. *See, e.g., Page 19, Line 21 to Page 20, Line 3.* In addition to this general guidance as to how to practice Applicants' claimed process, the Specification is replete with descriptions of working examples of Applicants' process. *See Specification, passim.*

With regard to the derivatives of GLP-1, Applicants submit that the amino acid sequence of GLP-1, 37 amino acid residues, is known. Thus, modification of the GLP-1 sequence by the skilled artisan to arrive at an appropriate derivative would be standard and is supported by the Specification, such that a GLP-1 derivative would not have an amino acid sequence with an unknown homology to human GLP-1. Furthermore, the Specification provides a lengthy list of derivatives of GLP-1, as well as methods of determining appropriate derivatives and discusses in detail GLP-1 derivatives, as well as providing detailed information with regard to amino acid substitutions. *See, e.g., Page 2, Line 22 to Page 3, Line 28; Page 13, Line 1 to Page 17, Line 2; and new Claims 94-133.*

In light of the above comments, Applicants respectfully submit that the Specification indicates that Applicants were in possession of the subject matter of new Claims 54-134, thereby satisfying the written description requirement of 35 U.S.C. § 112, First Paragraph.

Enablement

Claims 27, 29-40, 45, and 47-53 stand rejected under 35 U.S.C. § 112, First Paragraph, as purportedly lacking enablement. *See Official Action mailed July 1, 2004, Pages 6-8.* The Office admits that the application enables a process for

making derivative of *human* GLP-1 using fusion proteins shown at Figures 7, and 11-13 and fusion proteins wherein a given GLP-1 derivative is substituted by any of the GLP-1 derivatives recited in the Specification. *Id. at Page 6.* However, the Office asserts that the Specification does not reasonably provide enablement for a process of making a peptide of any structure and/or function or GLP-1 derivative using other helper and protective peptides. *Id. at Pages 6-7.* Applicants respectfully traverse these rejections.

Not to acquiesce in the Examiner's rejections, but solely to facilitate prosecution, Applicants have canceled rejected Claims 27, 29-40, 45, and 47-53 by the foregoing amendments. Accordingly, the 35 U.S.C. § 112, First Paragraph, enablement rejections have now been rendered moot.

Applicants respectfully submit that one of skill in the art can readily practice, and certainly without "undue experimentation," the subject matter of new Claims 54-134. As stated in *Ex parte Forman* (230 U.S.P.Q. 546 (1986)) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As the Office is aware, "[a] patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). To this end, Applicants submit that the guidance and specific examples set forth in Applicants' Specification, combined with what is known in the art, render the claims enabled.

The Office specifically asserts that while the Specification teaches a method for making a highly purified GLP-1 derivative, it does not provide guidance as to a process for producing a highly purified peptide of any function or characteristics. *Official Action mailed July 1, 2004, Page 6.*

Applicants submit that the claimed process provides a method of industrial production of a peptide of interest that utilizes, and then transiently alters, the native physicochemical properties of the peptide of interest. Prior to Applicants' invention, such production would result in problems such as yield, process control, and cost. To address these problems, the present process employs a fusion peptide comprising a helper peptide and the peptide of interest, with a protective peptide. First the fusion peptide is cleaved at a first cleavage site to remove the protective peptide in order to obtain an intermediate fusion peptide comprising a peptide of interest and a helper peptide. Next, the intermediate fusion peptide is purified. The helper peptide is present to improve the properties of the intermediate fusion peptide and to place it in the most advantageous configuration for the purification process.

Thus, for example, the structure of the helper peptide depends on the structure of the peptide of interest. During the purification, it is very important to control coagulation and precipitation, which depend on the acidity and hydrophobicity of the protein to be purified. Therefore, if the peptide of interest is too acidic, the helper peptide should be basic, and vice versa. Similarly, if the peptide of interest is too hydrophobic, then the helper peptide should be hydrophilic. Applicants note that the calculation of acidity and hydrophobicity, and thus the ability to easily determine the appropriate helper peptide, are readily available to the skilled artisan. For example, the software DNASIS (*see* "Trends in Analytical Chemistry," 5(4) 82-83

(1986)) was readily available at the time the instant application was filed. In addition, at present, software such as ExPASy (http://kr.expasy.org/tools/pitool.html and http://kr.expasy.org/cgi-bin/protscale.pl) is well known and readily available to those in the art.

Applicants further submit that the skilled artisan would be able to determine the appropriate protective peptide without undue experimentation. Protective peptides, such as *E. coli* β-galactosidase, glutathione transferase, and maltose-binding protein, are well known in the art.

Thus, Applicants submit that the peptides of the present invention can be easily determined and designed based on the selected peptide of interest. Once the peptide of interest is determined, the appropriate helper peptide is the one that will produce the most ideal isoelectric point range for the prevention of coagulation (pI 8-12) in combination with the peptide of interest. For example, if the helper peptide must be acidic to counteract the basic nature of the peptide of interest, then the helper peptide should contain a large amount of acidic amino acids, such as aspartic acid or glutamic acid. If a basic helper peptide is desired, then basic amino acids, such as arginine and lysine, should be used.

In light of the above comments, Applicants respectfully submit that the Specification readily allows those of skill in the art to practice the subject matter of new Claims 54-97, thereby satisfying the enablement requirement of 35 U.S.C. § 112, First Paragraph.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and Reply to Accompany Request for Continued Examination, or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (703) 836-6620 so that prosecution of the application may be expedited.

Respectfully submitted,
BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: July 5, 2005

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APPENDIX A

Instant New Claim	Corresponds at Least to Prior Claim as of March 29, 2004 or Support At Least At
54	29
55	30
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75	51
76	27
77	27
78	29
79	52
80	29
81	29
82	Figure 7
83	Figure 7
84	Figure 11
85	Figure 11
86	Figure 12
87	Figure 12
88	Figure 13
89	Figure 13
90	Example 12A; SEQ ID NO:5
91	Example 12B; SEQ ID NO:8
92	Page 2, Lines 22-33
93	Figure 7, SEQ ID NO:20
94	Page 13, Line 18 – Page 15, Line 24
95	Page 13, Line 18 – Page 15, Line 24

Instant New Claim	Corresponds at Least to Prior Claim as of March 29, 2004 or Support At Least At
96	Page 13, Line 18 – Page 15, Line 24
97	As described above for claims 54, and 82-91 and 93